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# Accurate, Safe & *Adequate* Agonist Dosing in Maintenance/Pain

Missouri Department of Mental Health

Spring Training Institute - May 19, 2006

## Methadone: Pain Management / Opioid Addiction Treatment

Most of this presentation applies to both applications for methadone, however the basic distinctions are critical.

The methadone effects relate to relief of pain AND prevention of the onset of opioid abstinence syndrome.

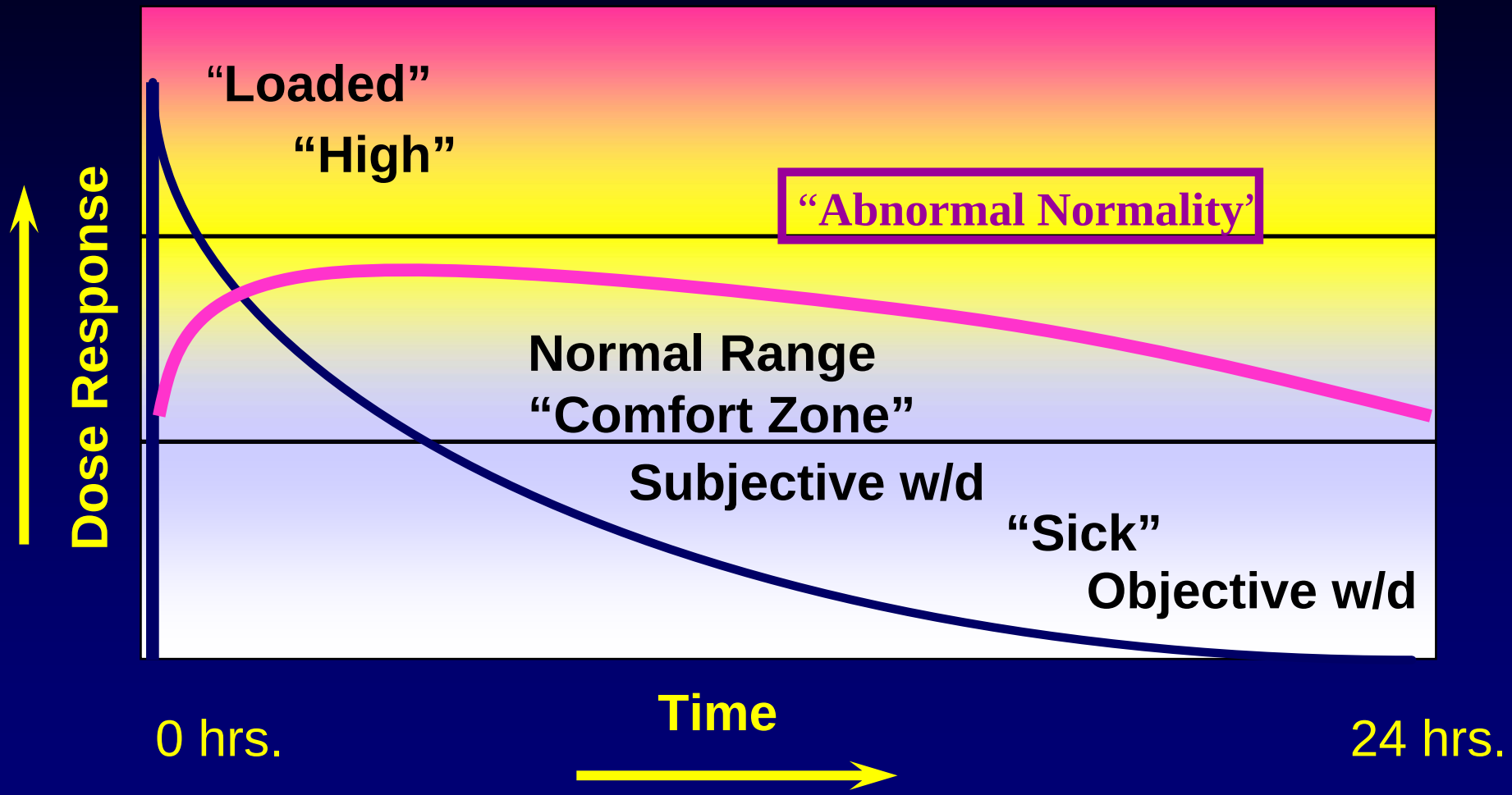
As an analgesic methadone is similar to morphine in terms of dose AND duration of effect (6-8 hours). Methadone is usually prescribed for dosing every 6-8 hours, that is *not* long acting .

When used to stabilize opioid addiction, most patients do well with a single dose every 24 hours.

# Pain Management During Maintenance Pharmacotherapy

- Continue maintenance without interruption
- Provide short-acting opioid analgesics as needed
- Higher doses may be required at increased frequency - titrated for relief of pain
- Do not use **Mixed Agonist/Antagonist** or partial or weak agonist drugs
- Monitor prescriptions closely

# Methadone Simulated 24 Hr. Dose/Response
# At steady-state in tolerant patient



# ADEQUATE DOSE DEFINED:

Prevention of onset of withdrawal syndrome for inter-dose interval, usually 24 hours or more...

Reduction or elimination of drug hunger or craving, inter-dose interval or more...

“Blockade” of euphoric effects of other opioid agonist associated with cross tolerance...

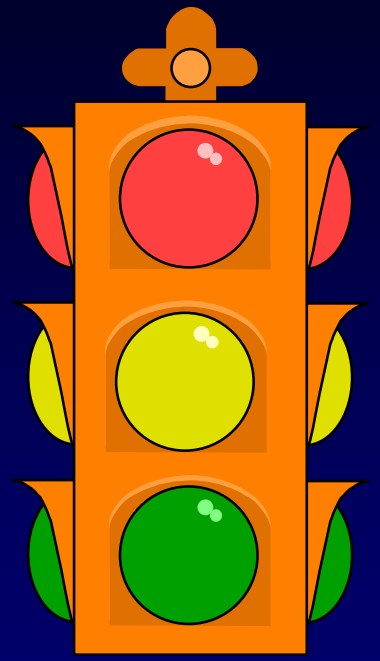
# ADEQUATE DOSE Depends on:

Steady-State occupation of a critical level of opioid receptors over dosing interval...

Blood level fluctuations are controlled as to prevent over or under-medication over the inter-dose interval...

# How Much?

# ENOUGH!!!



INDIVIDUALIZED !

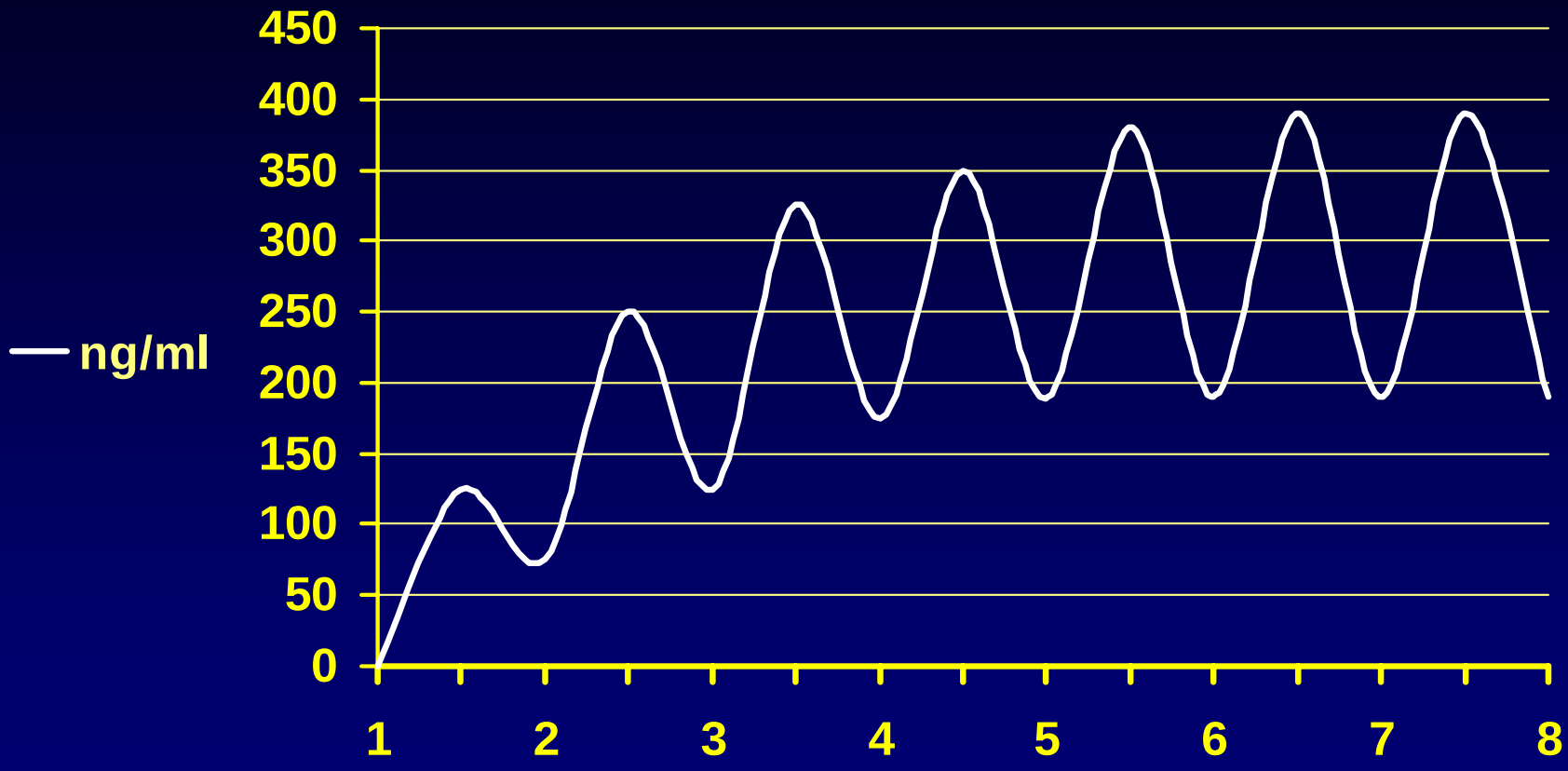
***ADEQUATE DOSE***

*… based on clinical response*

# ADEQUATE DOSE PHARMACOLOGY:

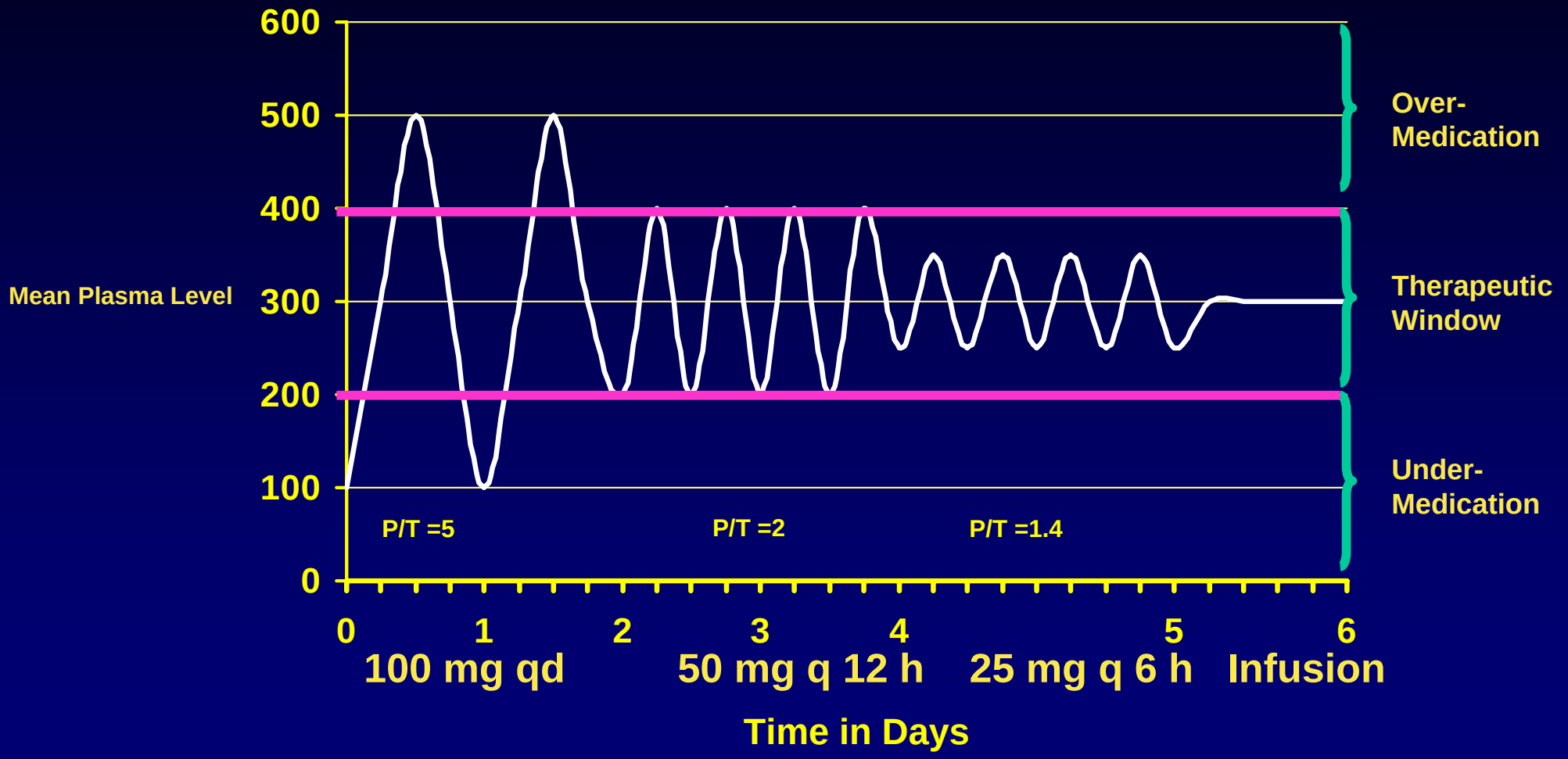
- Steady-state (build-up)
- Half-life (15-55 – Baselt)
- Fluctuations of levels (dose intervals)
- Metabolic variations (inter-individual and drug related)

# “Build-up” To Steady-State




**Days/Half-Lives (T-1/2=15-55 hrs.(Baselt))**
**Dose constant at 30 mg to steady-state**

# Steady-State – Fluctuations Determined by of Dose Interval




WHO Guide to Good Prescribing: Essentials of Pharmacology in Daily Practice. Annex 1.

http://www.docnet.org.uk/who/ggp/homepage.htm

# ADEQUACY OF DOSE IS BASED ON 2 FACTORS:

- The amount of medication (size of dose)

And

- The dosing interval (24,12, 8, hrs., etc.)

# How much is enough?

The amount required to produce the ***optimal response*** for the appropriate duration of time, with an allowance for a margin of effectiveness and safety.

# How much is too much?

More than the amount required to produce the ***optimal response,*** or a response that cannot be sustained without escalation of dose due to the continued development of tolerance; ("abnormal normality").

# Patient Expectations… Optimal Vs. Desired Response

The clinician and the patient must speak the same language to ensure ***realistic expectations*** and goals of OAT. A pattern of dose escalation in pursuit of the elusive state of “abnormal normality” must be recognized by the patient and the clinician.

# The Impossible Dream or "Abnormal Normality Syndrome"

…endless loop:

1. "My dose only holds me a few hours"
2. Increase dose
3. "The increase helped a lot for a few weeks but now it is not holding me – I need an increase."
4. Goto step 2.

# Maximum Dose?

Arbitrary dose ceilings have no foundation in science or clinical practice.

Dose caps are not supported by CSAT, AATOD, ASAM or any credible entity.

(See on-line version of Methadone-Drug Interactions – UPDATED at www.atforum.com for a better understanding of the wide dose variability seen in practice….)

# METHADONE BLOOD LEVELS

## why and why not?

## When and Where?

# SMLs

**The Relationship Between Mood State and Plasma Methadone Concentration in Maintenance Patients**

**Dyer KR, White JM, Foster DJR, Bochner F, Menelaou A, Somogyi AA. Royal Adelaide Hospital, Adelaide, Australia**

***Journal of Clinical Psychopharmacology,***
**2001 Vol 21(1):78-84.**

**This study demonstrates that significant mood changes occur in response to changes in methadone concentration, and these are more pronounced in "non-holders" (early onset withdrawal) than "holders" (stable for 24 hours).**

# SMLs -Dyer & Associates Continued

**The difference in w/d severity between self-reported holders and non-holders was not related to either methadone dose or trough plasma methadone concentration, demographic or other individual characteristics but, rather to the significantly more rapid rate of decline in plasma concentration during the period from the peak concentration until the trough.**

**…high peak/trough ratio**

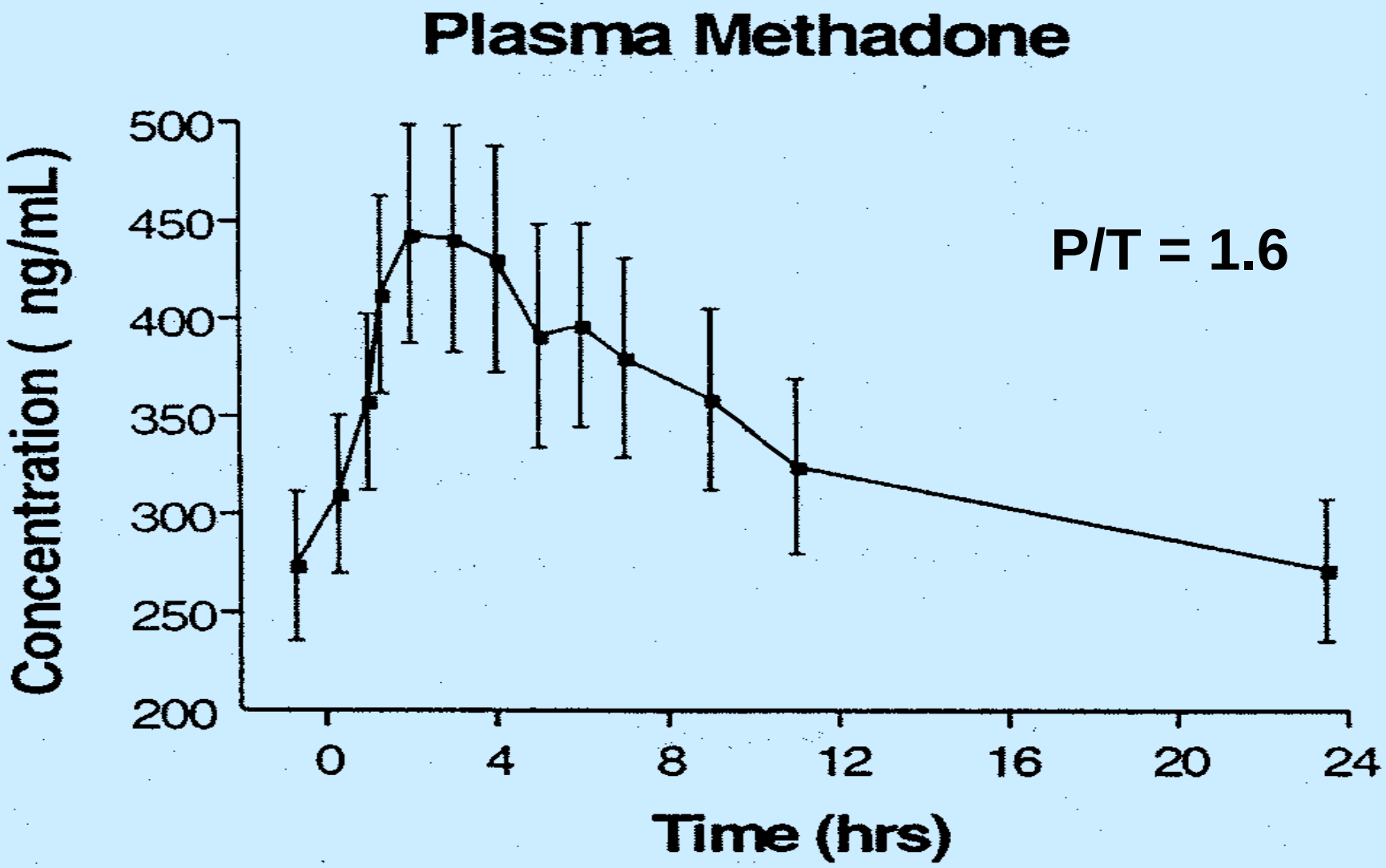
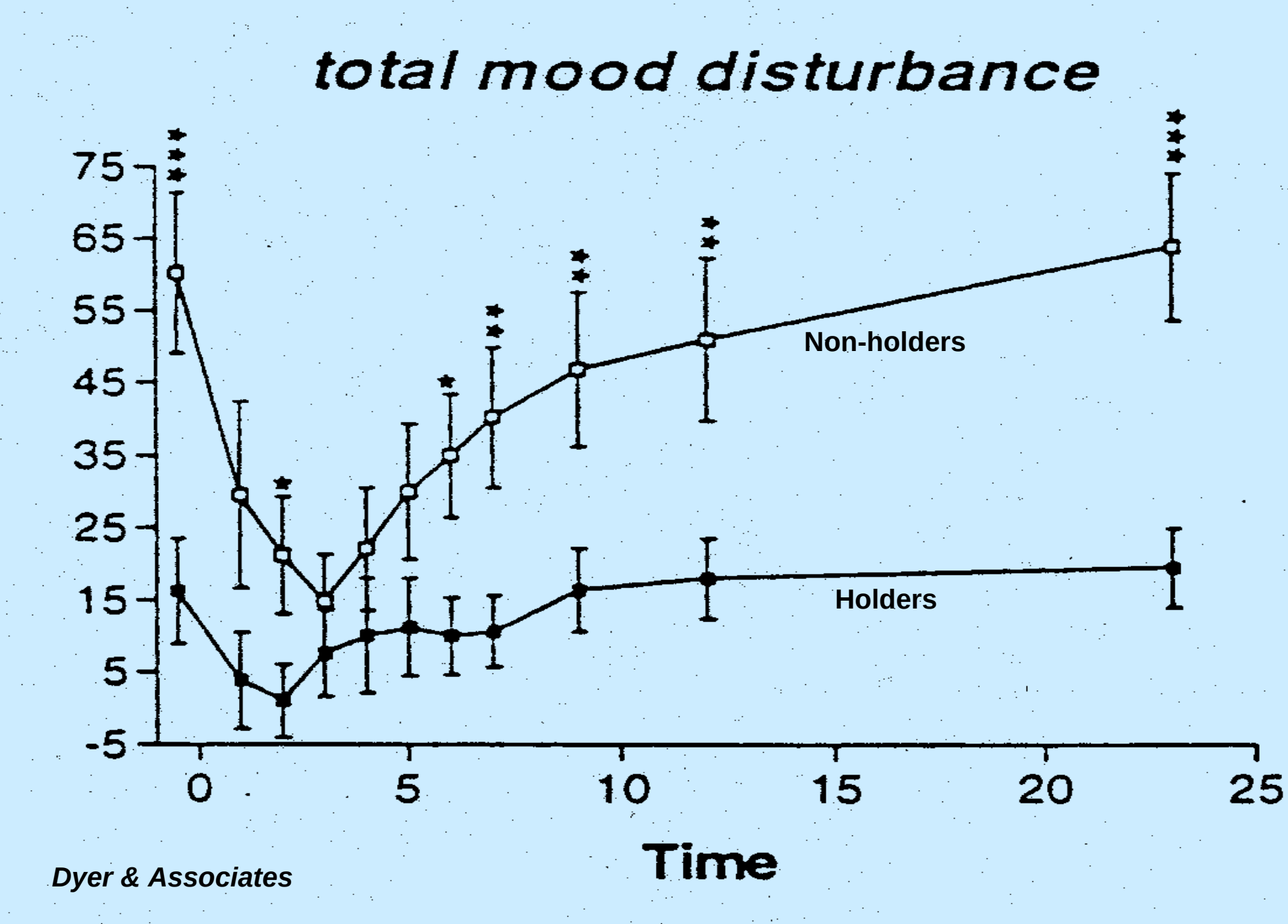



FIG. 1. Mean (± SEM) plasma methadone concentration-time profile during a single 24-hour interdosing interval in 18 methadone patients.


total mood disturbance
75
65
55
45
35
25
15
5
-5
0
5
10
15
20
25
Time
Non-holders
Holders
Dyer & Associates

# Serum Methadone Levels:

- **Do NOT indicate adequacy of dose**
- **Do Not predict methadone toxicity**
- Define Peak to Trough ratio, the rate of decline or metabolism
- Define the optimum dosing interval to maximize benefits of OMT
- Clinical Picture / Dose Incongruities
- Suspected Drug Interactions
- Justification of “unusual” dose levels/schedules
- Monitor effectiveness of divided dose schedules

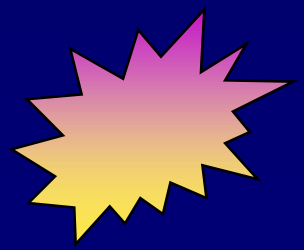
# Interpretation of Serum Methadone Levels

**Peak or trough Levels alone are of negligible clinical utility in determining adequacy or toxicity of a given dose.**

***Dose adequacy is determined clinically!***

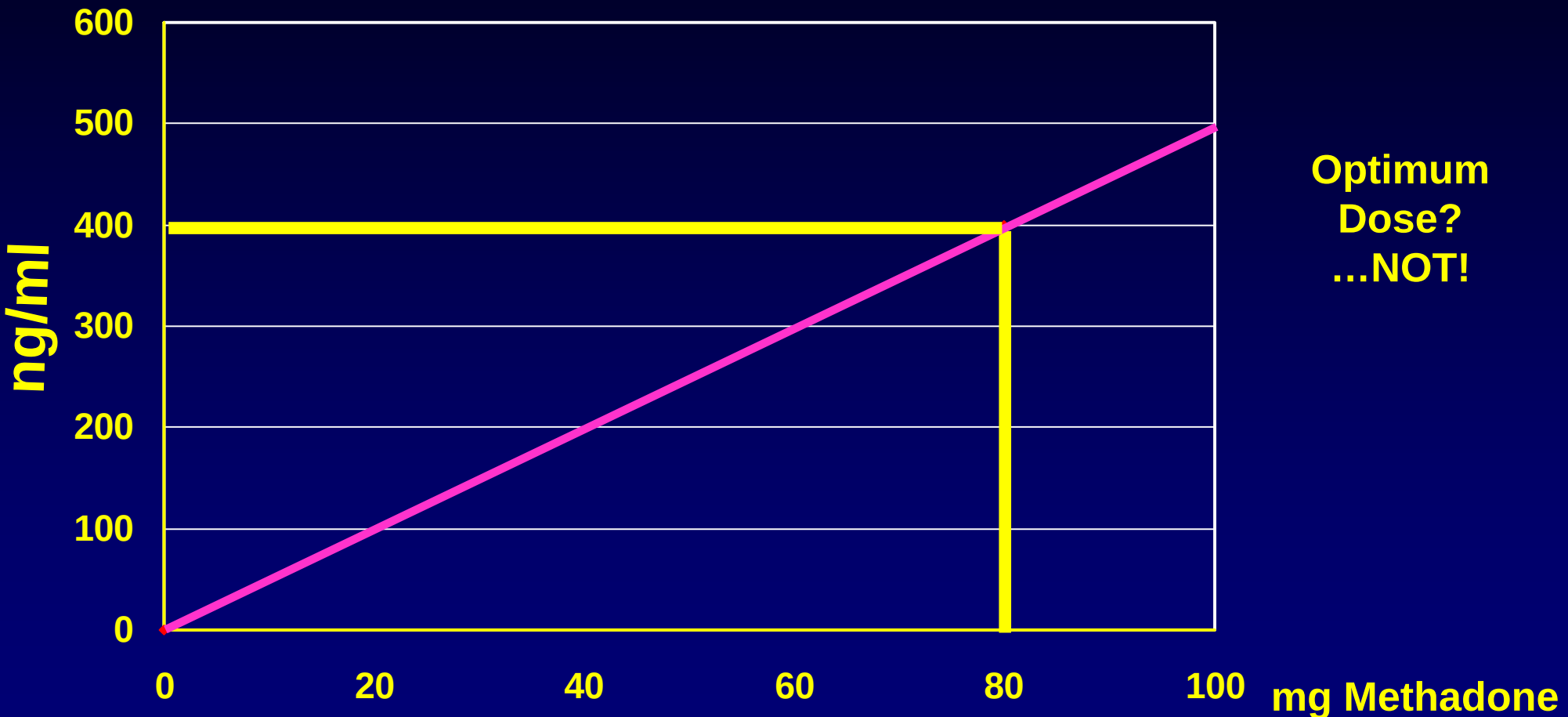
**(carefully question patient as to how they feel at different times of day, especially 3-4 hours & 24 hours.)**

**Peak/Trough Ratio ideally less than 2, 700/400=1.75, values > 2 suggest rapid metabolism, 800/200=4**



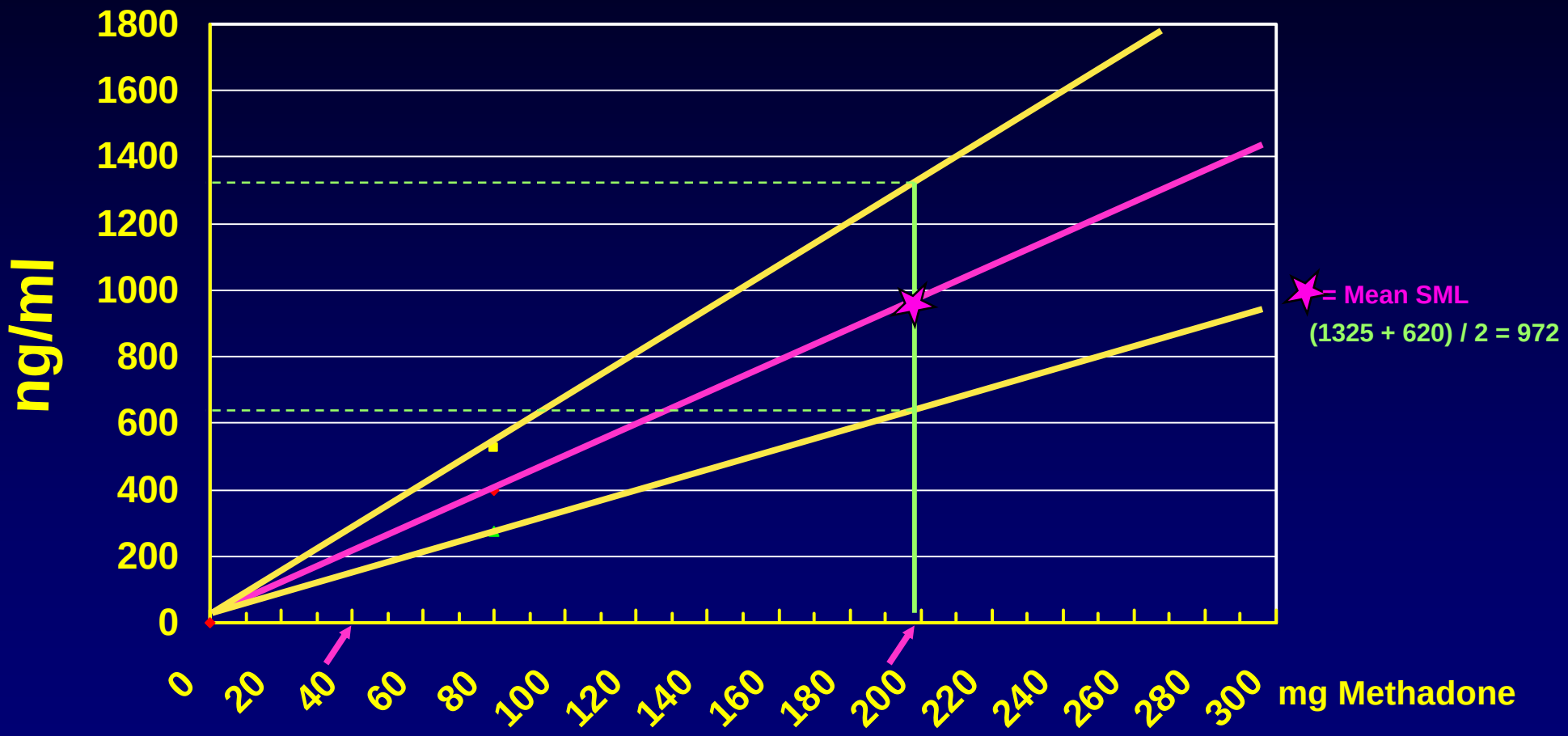
***Rate of change !***

# There is linear relationship between dose and methadone levels but NOT to clinical response



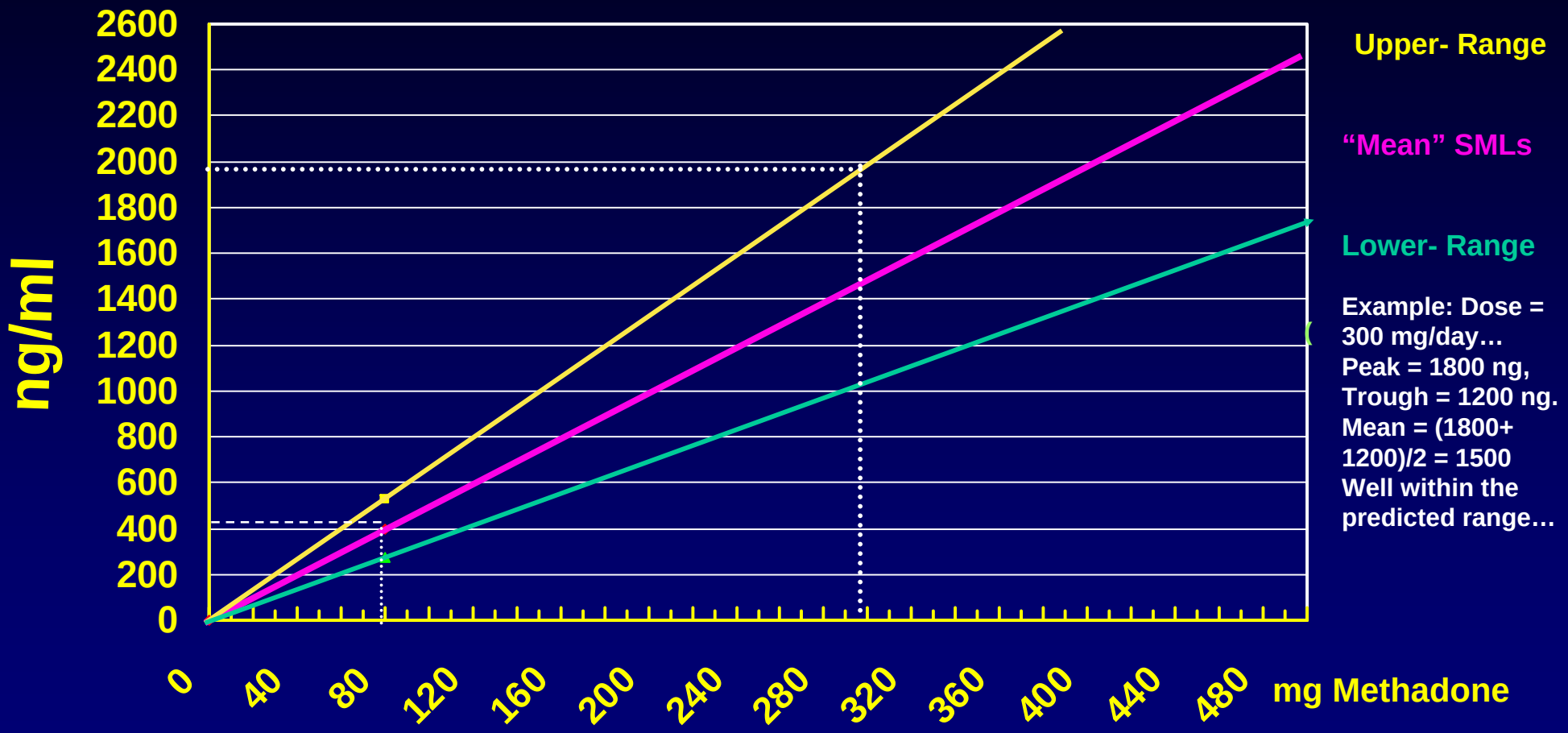

Payte & Khuri - Adapted from Wolff et al 1991

# Linear Relationship Methadone Dose / Mean Expected SMLs patient on 200 mg




Payte 2006- Adapted (extrapolated) from Wolff et al 1991

# Linear Relationship Methadone Dose / Mean Serum Methadone Levels & Range




Payte 2004 - Adapted from Wolff et al 1991

# Urinary pH Disposition of Methadone

| Urinary pH | 5.2 | 7.8 |
|---|---|---|
| Methadone Plasma Half-life | 19.5 +/- 3.6 hours | 42.1 +/- 8.8 hours |

Source: Nilsson et al., 1982

# My dose isn’t “holding” me

- Environment?
- Stressors?
- Alcohol?
- Other drugs/medications?
- Vitamins? (especially C)
- Urinary pH?
- Clinically adjust methadone dose
- Methadone blood levels?

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# “Not Holding” Strategies

- Cognitive, Behavioral Interventions
- Increased contact, counseling, therapy
- Alter urinary pH?
- Is patient fixing? - Raise dose
- Split Dose?

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# November 2005 Update/Revision, and release of *on-line version* of "Methadone-Drug Interactions"

http://www.ATForum.com

Click on the "Rx Methadone" tab

Scroll down to Methadone-Drug Interactions, then

Click on http:www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf

(Requires Acrobat Reader)

# METABOLIC BASICS:

- A ***substrate*** is any drug metabolized by one or more CYP enzymes, and more than half of all medications that undergo metabolism are CYP3A4 substrates (Piscitelli and Rodvold, 2001).

- Some drugs are ***inhibitors*** of specific CYP enzymes and thereby slow the metabolism of drugs that are substrates for those particular enzymes, which may result in excessively high drug levels and related toxic effects (Levy et al. 2000).

- Other drugs are ***inducers***; they boost the activity of specific CYP enzymes resulting in more rapid metabolism of suibstrate drugs, which may result in lwoer than expected levels of the substrate drugs (Flexner and Piscitelli 2000)

**Source: Leavitt, ATF, "Methadone-Drug Interactions"**

# METHADONE METABOLISM & DRUG INTERACTIONS:

# UNDERSTANDING THE BROAD VARIABILITY

- **"…there are more than 100,000 deaths annually attributed to reactions involving prescribed medications (Cohen 1999; Wilkenson 20050."**
- **"Three-fourths of those adverse reactions related to drug interactions,…(Bochner 2000; Levy et al. 2000; Piscitelli and Rodvold 2001)."**
- **"…there are more than 100 substances …that can interact in some fashion to affect a patient's respose to methadone (Leavitt 2005)."**

**Source: Leavitt, ATF, "Methadone-Drug Interactions"**

## Methadone Metabolism

Most Important Enzymes; CYP 3A4 and CYP 2B6

Others; CYP 2D6 and possible CYP1A2

"CYP3A4, the most abundant metabolic enzyme…, can vary 30-fold between individuals…(EAP et al; Leavitt et al. 2000)."

Also present in the intestine with 11-fold variability accounting for differences in breakdown and absorption of methadone (Levy et al. 2000).

Genetics: 1 of 15 lack CYP 2D6 and are very sensitive to methadone while those with high activity of the enzyme are rapid metabolizers of methadone.

**“The variability of CYP-enzyme presence and activity means that SMLs can differ significantly even in the absence of interacting substances; some persons can naturally be either extensive (rapid) or poor (slow) metabolizers of methadone. When interactions with other drugs occur on top of this it could further influence problematic methadone under- or overmedication ( Eap et al. 2002; Leavitt et al. 2000; Richelson 1997).”**

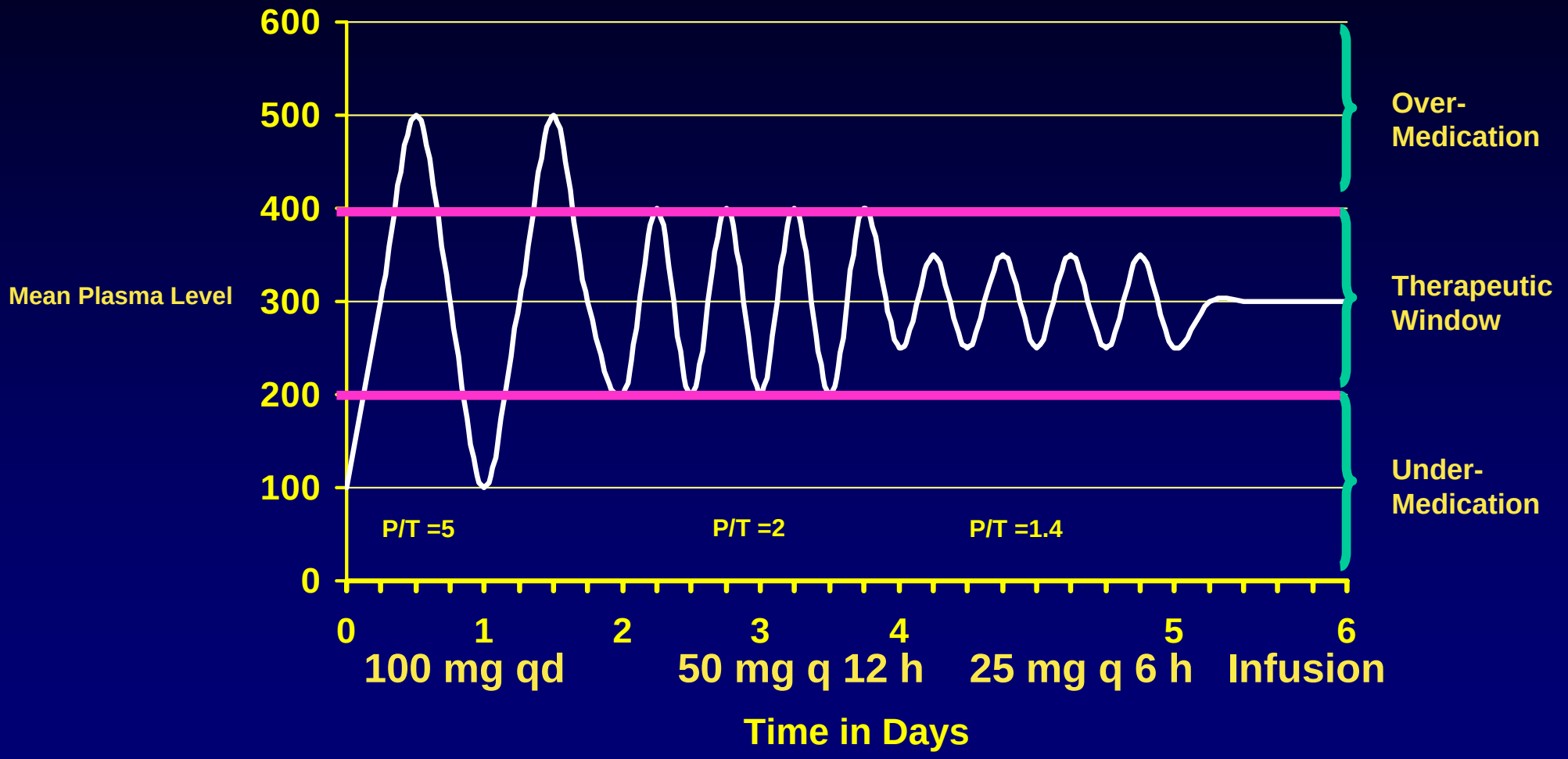
# Cytochrome P-450 Enzyme Activity
## Drug Interactions - Methadone

- Induction
  - Rifampin
  - Phenytoin
  - Ethyl Alcohol
  - Barbiturates
  - Carbamazepine
  - Nevirapine (Viramune)

# Cytochrome P-450 Enzyme Activity
## Drug Interactions - Methadone

- Inhibition
  - Fluconazole
  - Cimetidine
  - Erythromycin
  - Fluvoxamine (Luvox)
  - Ketoconazole
  - Nefazodone (Serzone)
  - Ritonavir (Norvir)

# Steady-State – Fluctuations Determined by of Dose Interval

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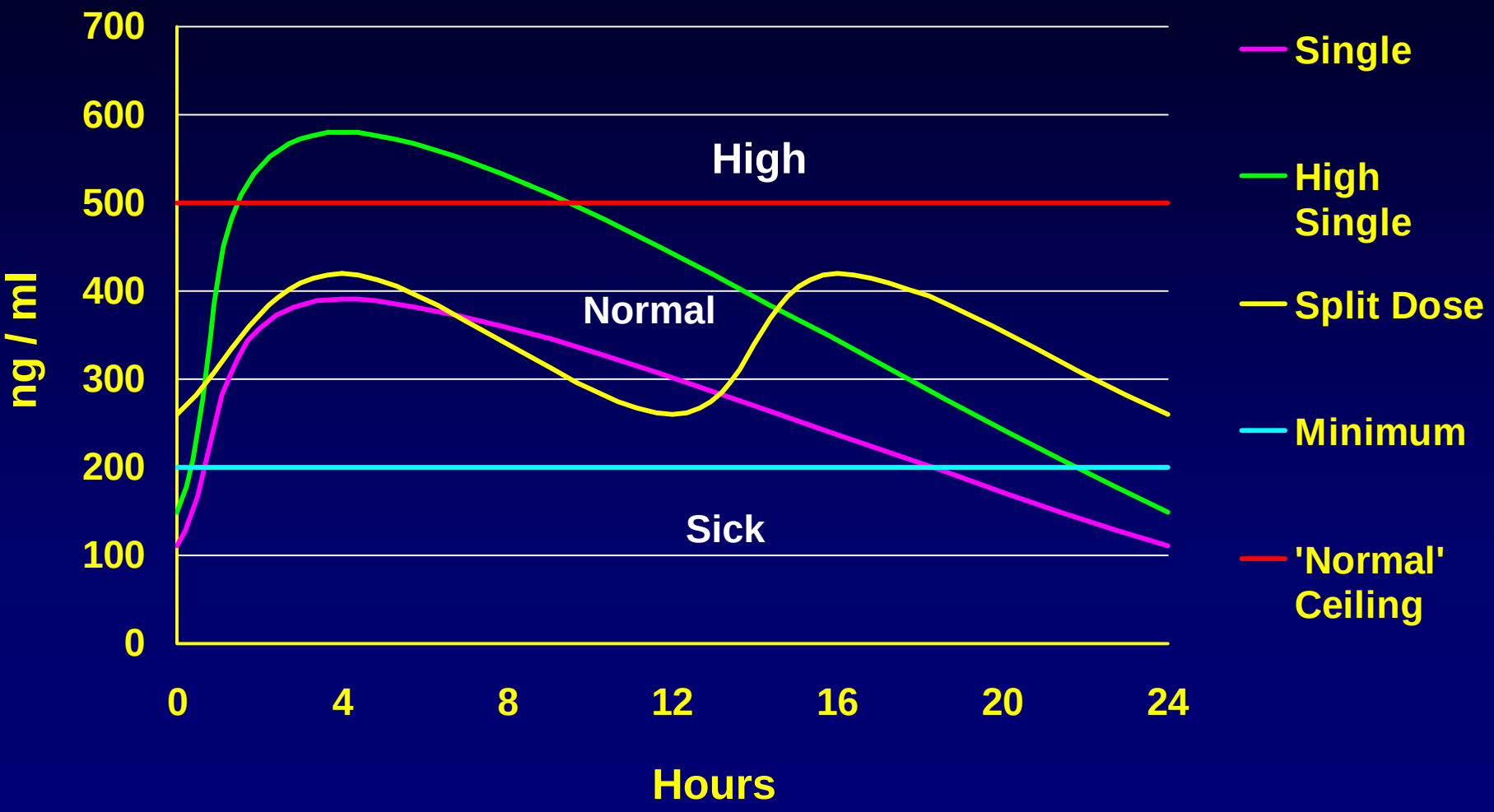
# Applications of preceding

Patient c/o waking up sick daily but is sedated 3-6 hrs. after dose:

Dose increase will not make the dose last longer, just increase the fluctuation between over and under medication.

Increase frequency not dose!

# Rapid Metabolizer - High Single and Split Dose Simulation



# Split Dose Induction
## (For patients feeling OK through the day but getting sick by bedtime & worse by morning)

- Day 1: 100% of current dose, observed, & 50% of dose to take in 12 hours

- Day 2 and beyond: 50% of dose q 12 h

*Note: Poor results from starting with half the usual dose on day 1*

# Split Dose Induction

**(For patients *sedated* at 3-4 hours after single dose)**

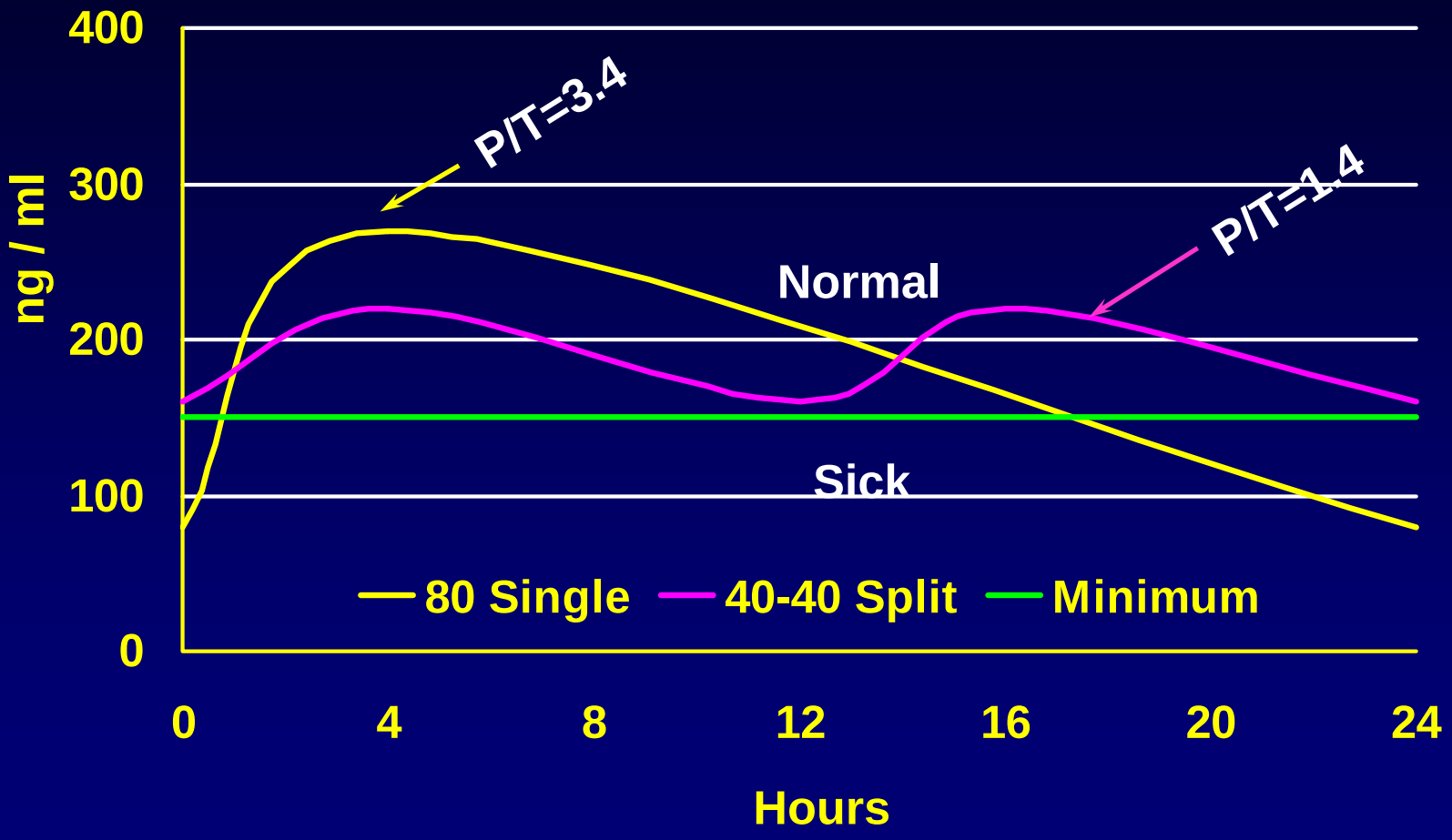
- Day 1: 60% of current dose observed
  50% of current dose to take in 12 hrs.

- Day 2 and beyond: 50% of dose q 12 h
  (titrated up or down as needed).

*Note: On day 1 some patients will do better with 60% for 2nd dose (120% of usual daily dose, 1st day only)*

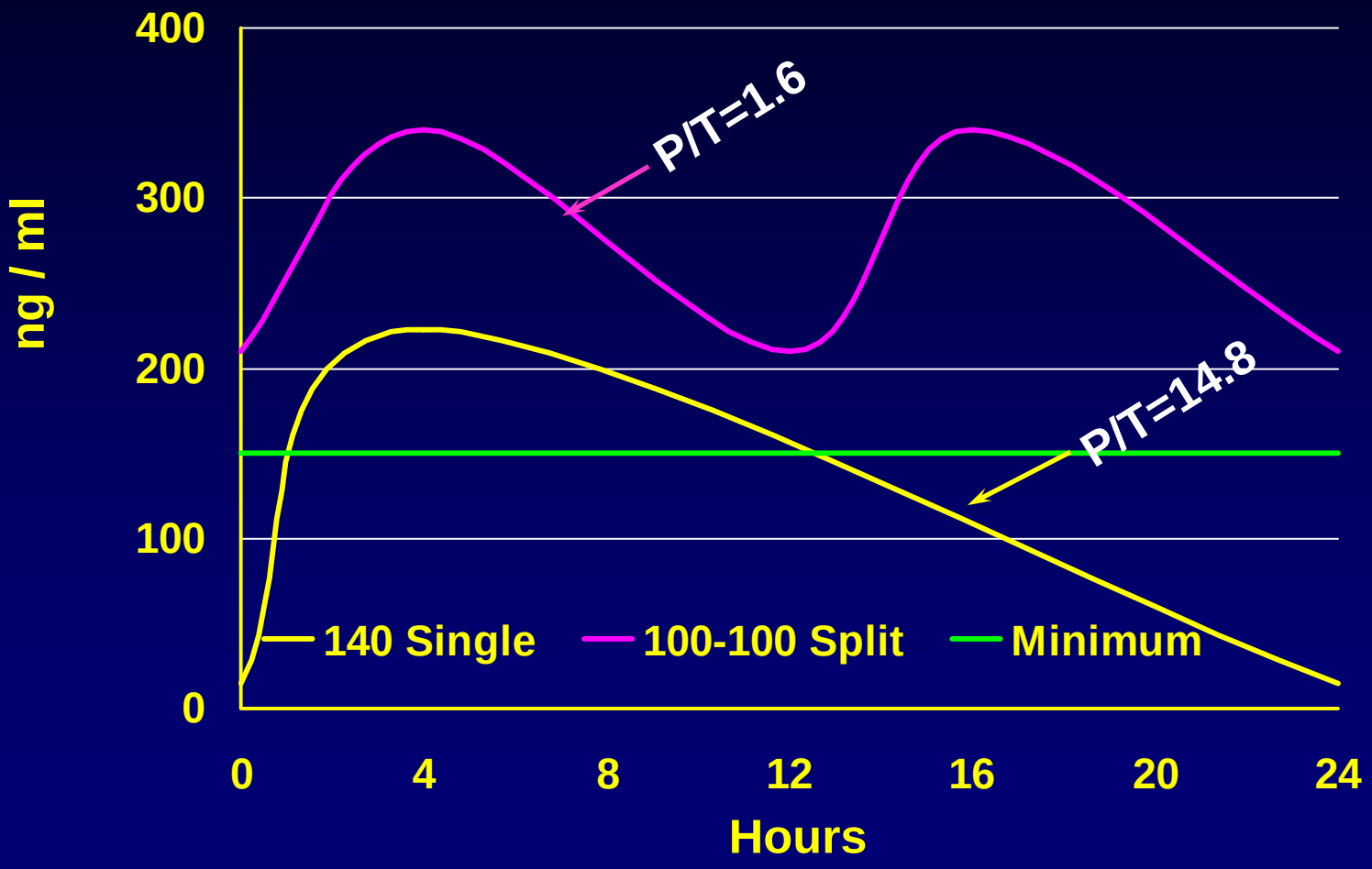
# Pregnancy Case Study @ 6 mo.

## " I wake up sick & my baby moves a lot!"

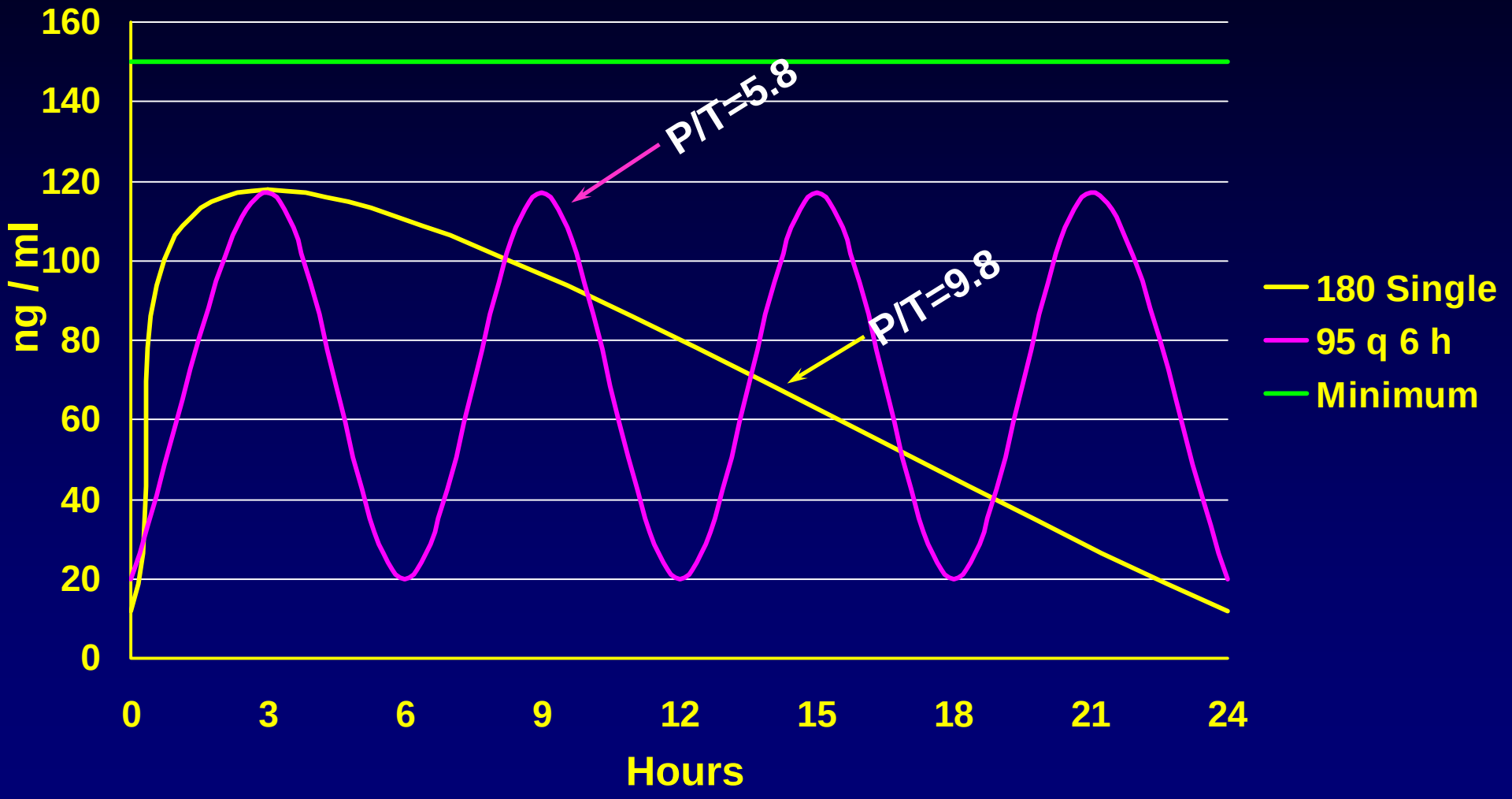


# Phenytoin Case Study

## "You can't be sick - you are on 100 mg!"



# Carbamazepine Case Study



# 2- Carbamazepine Case Study

## Methadone q 6 h + cimetidine